RADIATION BIOCHEMISTRY

K. I. Altman, G. B. Gerber, and S. Okada

Volume II: Tissues and Body Fluids

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Volume II: Tissues and Body Fluids
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We dedicate this book to Louis H. Hempelmann

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FOREWORD

A comprehensive review of the broad field of radiation biochemistry such as is presented in this treatise is long overdue. Studies of radiation biochemistry on the molecular and cellular level are now in vogue, due, in part, to new techniques, such as mammalian cell cultures and gradient centrifugation, now available for this type of experimentation. The intensive pursuit of studies in this field has led to discoveries that had only been dreamed of fifteen years ago. Although biochemical changes in tissues and body fluids of irradiated individuals are the sum of the molecular and cellular events throughout the body, there has been little effort to integrate these two aspects of radiation biochemistry or to explain the former changes in terms of the latter. As a result, interest in radiation biochemistry on the body and tissue level has declined in favor of the more basic cellular and molecular radiation biochemistry. This is illustrated by the relatively few biochemists now working on the gross metabolic phenomena caused by radiation exposure.

The main purpose of this work is to review critically the field of radiation biochemistry at all levels and to explain the observations at the body and tissue levels in terms of what is happening at the molecular and cellular levels. It is hoped that such an integrated approach will encourage interest in gross biochemical changes following irradiation. It is hoped also that the discussions in the text and the simplified schematic representation of gross biochemical changes may clarify the complex and sometimes contradictory reports in the literature. And, finally, it is my personal hope that repeated reference to possible biochemical indicators of radiation injury may stimulate work in this

field and lead to the discovery of a simple, yet accurate, practical measure of acute radiation injury in man.

Since the biochemistry of the metabolic changes induced by radiation exposure is a complex subject fraught with many pitfalls, this treatise should be of enormous help to life scientists who are just embarking in the field of radiation biology. In particular, the discussions of the complications introduced by body changes secondary to radiation damage, such as partial starvation and changes in cell populations of a given tissue, should aid in avoiding errors in interpretation that have been committed in the past. Hopefully this will encourage more scientists to enter the field of radiation biochemistry.

This book represents an enormous investment of time and energy on the part of the authors. I trust that other readers will find it as useful as I have.

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PREFACE

In our opinion, radiation biochemistry has three major aims: to describe radiobiological effects in biochemical terms; to elucidate the mechanisms underlying these effects; and to shed light on general biological principles in living organisms. In this two-volume treatise, we have tried to fulfill these aims to the best of our ability.

Because of space limitation, however, we have focused on the radiation biochemistry of mammalian systems, and cite only selected publications, a practice which is certain to result in the unjust omission of many important investigations. We have made a special effort to avoid mere descriptions of radiation-induced biochemical changes and have sought to seek correlations between the various biochemical changes and to interpret radiobiological effects at all levels in biochemical terms.

Volume I, written by Shigefumi Okada, shows the interplay among radiation chemistry, radiation biochemistry, radiation biophysics, and radiobiology which has brought us to our present understanding of cellular radiobiological effects in terms of molecules. The important feature of the interplay is the eradication of the demarcation lines between the disciplines of physics, chemistry, and biology. What excites many radiobiologists is the fact that the concepts developed through intensive radiobiological studies have had great bearing on the life sciences in general. These concepts involve hydrated electrons, DNA repair, artificially induced mutation, cell cycle, cell proliferation kinetics, and organ transplantation.

Volume II, written by Georg B. Gerber and Kurt I. Altman, deals with the

radiation biochemistry of mammalian organs and body fluids. Emphasis is placed on descriptions of overall biochemical changes in irradiated tissues and animals, on the dependency of these changes on cellular responses, and on the interactions among different organ systems. Consideration is also given to a practical application of radiation biochemistry to the problem of assessing the nature, tissue localization, and extent of radiation injury in man and animals.

It is hoped that this work will be useful to radiobiologists at all stages of sophistication as well as to other scientists who are interested in radiobiology. It is also hoped that it will illustrate a unique facet of radiobiology in which one type of environmental insult to mankind has been studied at all levels, individually and integrated, i.e., molecular, cellular, tissue, and whole body. This may serve as a guideline for future studies of many other types of environmental insults besides ionizing radiation. We sincerely hope that readers will sense our feeling of excitement about radiation biochemistry.

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June, 1970

KURT I. ALTMAN
GEORG B. GERBER
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CELLS

Chapter I

GENERAL ASPECTS OF RADIATION BIOCHEMISTRY

A. Introduction

A delineation of the biochemical response of mammalian organisms to radiation must touch upon several levels: (a) it must define the biological events in the cell at the molecular level, as was attempted in Volume I of this treatise; (b) it must integrate the cellular events with the changes occurring in individual organs; (c) it must take into account the interaction between the different cells and organs and the humoral and nervous regulators of metabolism. From the beginning, radiation biology emphasized the morphological sequelae of irradiation as seen grossly or with the microscope. Recently the dynamic concept of the renewal of cells and their constituent molecules has been added to these static aspects of radiation damage. A quantitative account of the behavior of metabolic activity and its regulation is still a distant goal in radiation biology. Progress toward this goal can be achieved only to a limited extent because structure and biological function are not separate entities, but two aspects of the same picture.

This chapter introduces several basic notions of mammalian radiation biology and then points out the pitfalls and opportunities inherent in design and interpretation of experiments in radiation biochemistry.

B. Whole-Body and Local Irradiation

1. Whole-Body Irradiation

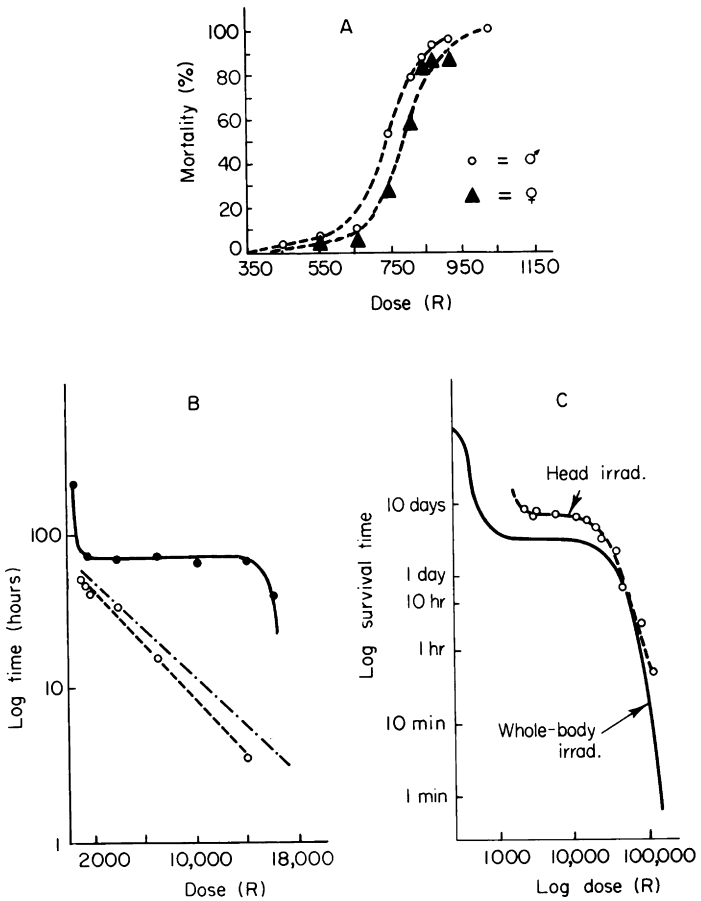

FIG. I-1. (A) Mortality of male and female mice after whole-body irradiation. [From W. H. Chapman, *Radiation Res.* **2**, 502 (1955).] (B) Mean survival time of normal, adrenalectomized, and hypophysectomized rats after whole-body irradiation: solid line—control; dash line—hypophysectomized; dot-dashed line—adrenalectomized. [From G. Gerber, "Wissenschaftliche Grundlagen des Strahlenschutzes," pp. 149–162, 1957.] (see also *10*). (C) Mean survival time of male mice after whole-body or head irradiation. [From B. Rajewski, K. Aurand, and O. Heuse, *Z. Naturforsch.* **8b**, 524 (1953).] Female mice are more radioresistant than male ones. The dose-independent survival time after doses causing gastrointestinal death becomes dependent on the dose in adrenalectomized or hypophysectomized rats. The survival time after head irradiation is independent of the dose but longer (about 9 days) than that after whole-body irradiation (3.5 days). Above 30 kR the curves for head and whole-body exposure coincide.

Exposure to ionizing radiation of the whole body or of large parts of the mammalian organism produces a characteristic sequence of acute symptoms which depend on the radiation dose (*3*). (i) Relatively low doses of radiation (up to about 1000 R) damage primarily the blood-forming tissues (see Chapter II). The renewal of stem cells in the bone marrow is impaired and widespread cell death occurs in lymphoid tissue. This injury to the cellular and immunological defense mechanisms of the organism may cause death as a result of infection, bleeding, or anemia from 1 to several weeks after exposure. Exposure to radiation which does not produce death within a few weeks may shorten the life-span by accelerating the unspecific processes of aging or by inducing cancer and leukemia. (ii) In the dose range from 1 kR to about 10 kR, cell renewal in the gastrointestinal tract is severely disturbed and the animals die shortly after the epithelial lining of the intestinal villi has been lost (3–7 days after exposure), presumably as a consequence of the loss of electrolytes and water. The survival time for gastrointestinal death is dose-independent (Fig. I-1). (iii) After still higher doses, injury to the central nervous system (see Chapter IX, I) plays the predominant role. Again, the survival time depends on the dose and, in mice, varies from almost 3 days after a dose of 20 kR to a few minutes after a dose of 100 kR (Fig. I-1). Death usually intervenes following convulsions and coma.

2. Local Irradiation

Local irradiation can produce a variety of symptoms, depending on the radiation dose and on the tissues exposed. If an organ responsible for death after whole-body irradiation (e.g., intestine or central nervous system) is submitted to local exposure, the symptoms will be similar to those seen after whole-body exposure (Fig. I-1). Uncommon modes of acute death can occur after radiation injury of other vital organs or areas (e.g., skin, kidney, and lungs). Most frequently, local symptoms predominate after local irradiation, and the outcome depends on the extent of the local tissue destruction, vascular damage, and fibrosis, and on possible late malignant changes.

The decision whether whole-body or local irradiation should be used in a biochemical investigation, depends, of course, on the particular problem being studied. Whole-body exposure is a simple and reproducible procedure, and is best suited for studies related to radiation illness. Local irradiation can be used in the examination of biochemical changes in a given organ. Local irradiation alleviates or eliminates the intervention by other organs and systemic reactions and, except at very high dose levels, circumvents the difficult problem of dietary controls (see p. 6). Thus, biochemical effects of radiation in organs can be studied for long periods or at relatively high dose levels. On the

other hand, local irradiation usually requires restraining or anesthetizing the animals, and these factors must be considered in the interpretation of the data.

C. Conditions of Irradiation and Experimental Controls

Biochemical alterations due to radiation exposure have to be distinguished from those due to factors secondary to the exposure procedure. The radiation insult should therefore be administered in a reproducible manner and controls should be provided to eliminate extraneous factors. The conditions of radiation

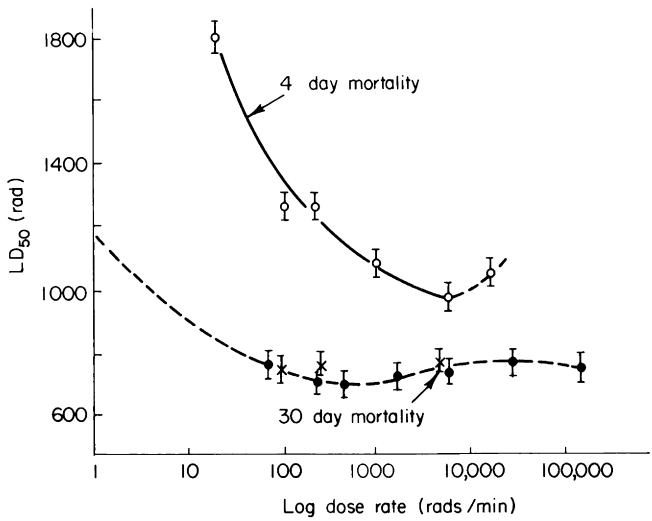

FIG. I-2. The 4- and 30-day mortality of mice (LD_{50}) after irradiation at different dose rates. Note that at high dose rates, mice become more sensitive to the gastrointestinal syndrome but not to the bone marrow death. [From S. Hornsey and T. Alper, *Nature* **210**, 212 (1966)] (see also *10a*, *26*).

should be chosen so as to ensure a homogeneous exposure of the volume desired and to reduce the stray radiation outside this volume to a minimum. In publications, one should present information not only about the dose but also about the dose rate (see Fig. I-2), the kilovoltage of x-rays, the filtering (or half-value layer), and the source to target distance.

Irradiation involves handling and restraining the animals, factors which, as such, may elicit a biochemical stress response. Control animals should, therefore, be sham-irradiated under the same conditions and at the same time as the animals are x-irradiated. Preconditioning the animals to the exposure conditions can substantially reduce the stress response to sham irradiation